Pergamon

Tetrahedron Vol. 51, No. 1, pp. 295-306, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)00956-2

Sequential and Cascade 1,3-Dipolar Cycloaddition-Palladium Catalysed Carbonylation-Cyclisation Reactions. Diastereospecific and Homochiral Processes.

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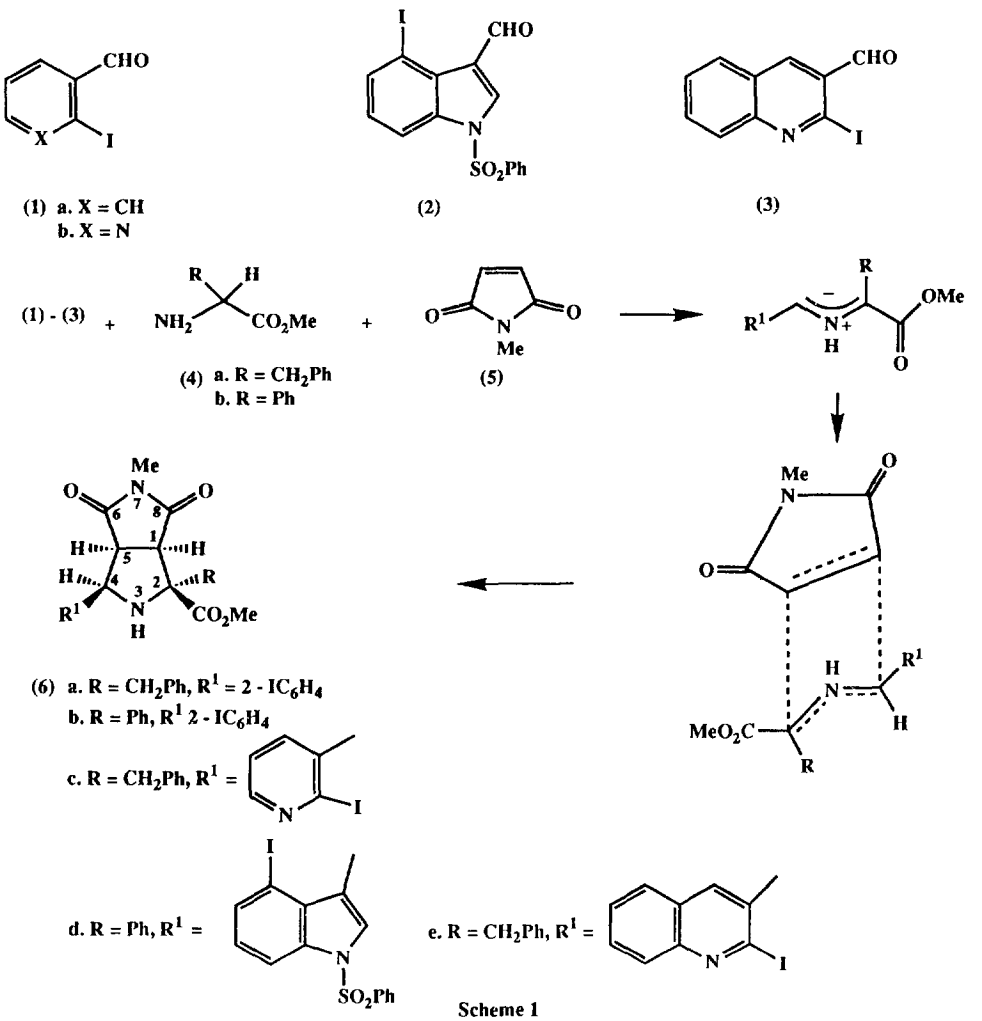
Abstract. Combinations of imine → azomethine ylide → cycloaddition cascades with Pd(0) catalysed cyclisation -carbonylation forming 5- and 6-membered lactams in sequential reactions are described and both diastereo-specific and homochiral examples are provided. The azomethine ylides can be generated either via thermal 1,2-prototropy or metal ion catalysis at ambient temperature. The former sequence has been combined with the Pd(0) catalysed cascade into a one-pot protocol.

We have developed a wide range of novel regio- and stereo-specific methodology involving imine → azomethine ylide → cycloaddition[1] and oxime → nitrone → cycloaddition cascade processes.[2] Chiral versions of these cascades have been[3-5], and are being created. In unrelated studies we have reported a range of palladium catalysed cascade ring forming processes involving concomitant carbonylation[6,7] and/or anion capture[8]. These two groups of reactions provide a series of opportunities for linking two disparate ring forming reactions in novel sequential or cascade Tactical Combinations which potentially offer highly efficient and selective protocols. Such protocols can provide one-pot access to target molecules possessing a high degree of complexity which would otherwise require technically demanding multistep syntheses. We have previously reported one such Tactical Combination which combined imine→azomethine ylide → cycloaddition cascades with intramolecular Heck reactions.[9] We now report the combination of imine → azomethine ylide → cycloaddition cascades with palladium catalysed carbonylation-cyclisation processes.

The imine → azomethine ylide → cycloaddition can be carried out under thermal activation or via catalysis employing a wide range of metal ions [e.g. Ag(I), Tl(I), Li(I), Co(II), Mg(II) etc].[1] In the former case the azomethine ylides are generated via 1,2-prototropy whilst the latter cascade involves metallo-azomethine ylides.[1]

A series of sequential reactions was explored first utilising thermal 1,2-prototropy to generate the syn- or E,E- azomethine ylides stereospecifically (Scheme 1). The aldehydes (1) - (3) react (toluene, 110 °C, 24h) with amino esters (4a,b) and N-methylmaleimide (NMM)(5) to give cycloadducts (6a-e)(Scheme 1) stereospecifically via endo-transition states and in good yield (Table 1). These cycloadducts react (MeCN, 80 °C, 60h) with a Pd(0) catalyst and CO(1atm) in the presence of TlOAc (1.2 equiv) to give products arising from carbonylation and subsequent intramolecular capture of the acylpalladium(II) species by the pyrrolidine nitrogen atom (Scheme 2).[10] The Pd(0) catalyst is generated in situ from 10mol% $Pd(OAc)_2$ and 20mol% PPh_3. The TlOAc is added to promote the carbonylation at atmospheric pressure.[6] Thus (6a-c) give (7a-c), (6d) gives

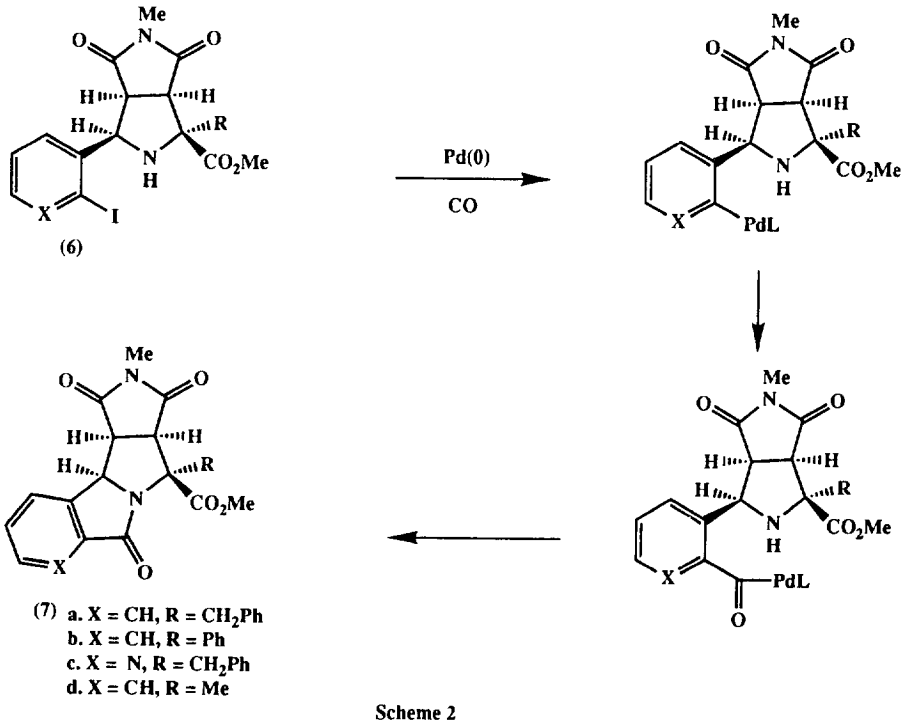
(8) and (6c) gives (9) all in good yield (Table 1).



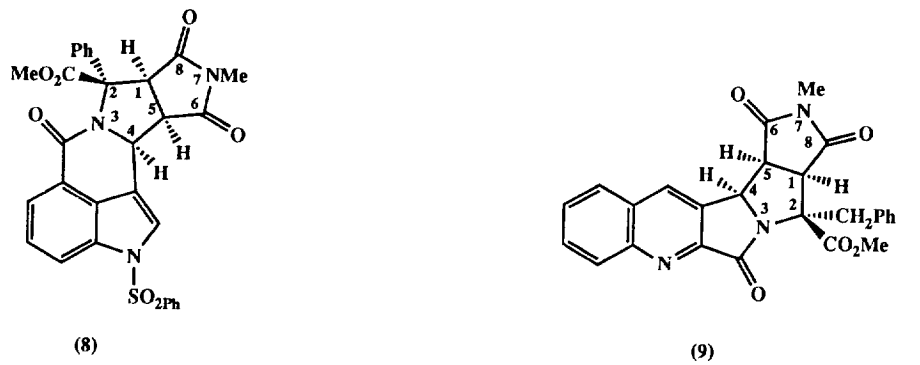
Scheme 1

Table 1. Sequential Thermal Cycloaddition-Palladium Catalysed Carbonylation-Cyclisation Reactions.

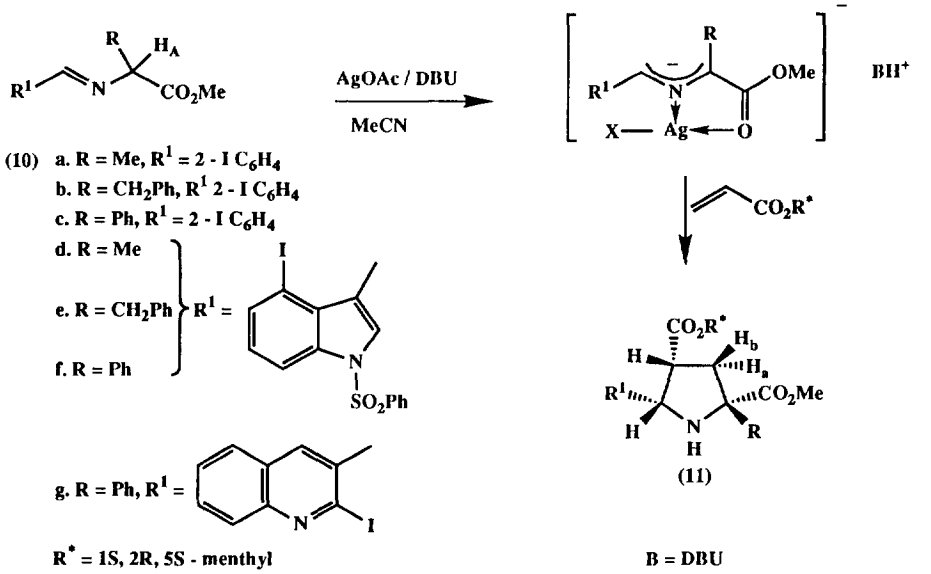
Aldehyde	Amino Ester	Cycloadduct	Yield(%)	Carbonylation Product	Yield(%)
1a	4a	6a	75	7a	70
1a	4b	6b	70	7b	60
1b	4a	6c	80	7c	70
2	4b	6d	72	8	60
3	4a	6e	85	9	73



Scheme 2



A second series of sequential processes employing metallo-azomethine ylides[1] and incorporating our recently reported chiral cycloaddition protocol[4,11] was then developed (Table 2). Metallo-azomethine ylide generation and cycloaddition is readily achieved at ambient temperature by a combination of silver acetate and DBU.[11,12] Thus imines (10a-g) undergo stereo- and regio-specific cycloaddition (MeCN, 25 °C) to (1S, 2R, 5S)-menthyl acrylate to give the homochiral cycloadducts (11a-g) (Table 2) via formation of the syn- or E,E-metallodipole (Scheme 3) and an endo-transition state.[12]



(10) a. R = Me, R^1 = 2 - I C_6H_4
b. R = CH_2Ph, R^1 2 - I C_6H_4
c. R = Ph, R^1 = 2 - I C_6H_4
d. R = Me
e. R = CH_2Ph } R^1 =
f. R = Ph

g. R = Ph, R^1 =

R^* = 1S, 2R, 5S - menthyl

Scheme 3

Table 2. Sequential Metallo-azomethine Ylide Cycloaddition-Palladium Catalysed Carbonylation-Cyclisation Reactions.

Imine	Time(h)	Cycloadduct[a]	Yield(%)	Carbonylation Product	Yield(%)
10a	4	11a	50	13a	70
10b	3	11b	52	13b	72
10c	1.5	11c[b]	86	13c	69
10d	3.5	11d	52	15a	69
10e	2.5	11e	51	15b	68
10f	2	11f[b]	80	15c	73
10g	1.5	11g[b]	84	17	74

a. Cycloadditions carried out in MeCN in the presence of AgOAc (1.5mol) and DBU (1.1mol) unless otherwise noted.

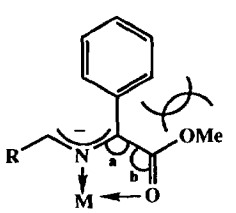
b. Catalyst comprised LiBr (1.5mol) and 2-t-butyl tetramethylguanidine (1.1mol).

The failure of the AgOAc/DBU combination to effect the cycloaddition of (10c), (10f) and (10g) and the effectiveness of LiBr/t-butyl tetramethylguanidine is believed to be due to steric factors arising in formation of the chelated metallodipole. The Ag(I) cation (ionic radius 1.26Å) is considerably larger than the lithium cation (ionic radius 0.68Å). In a chelated metallodipole (12a) the large Ag(I) ion causes the angles a and b to increase generating steric compression between the phenyl and methoxy groups. Twisting of the phenyl ring out of the plane of the azomethine ylide would both disrupt conjugation [effect on pka of H_A in chelated imine

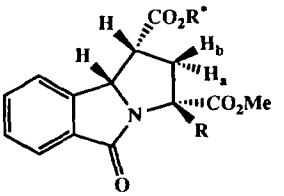
(10a)] and sterically hinder the cycloaddition. The small lithium cation allows any steric compression between the phenyl and methoxy groups to be accommodated by a decrease in the angles a and b.

The absolute configuration of the cycloadducts (11a-g) is assigned as the 2S, 4R, 5S-stereoisomer based, by analogy, on the absolute configuration of two cycloadducts of 1R, 2S, 5R-menthyl acrylate which were established by X-ray crystallography.[4,11]

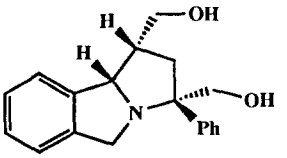
Carbonylation of (11a-c) afforded homochiral (13a-c), (11d-f) afforded homochiral (15a-c) and (11g) similarly afforded homochiral (17). In each of the two main series one example of a lactam diester was reduced to the diol with lithium aluminium hydride. Thus (13c) gave (14)(66%) and (15c) gave (16)(60%).



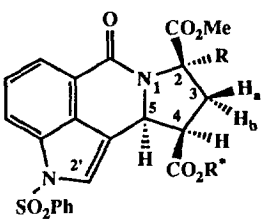
(12) a. M = Ag
b. M = Li



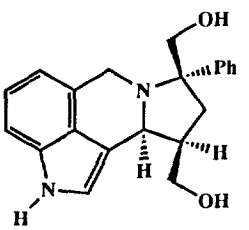
(13) a. R = Me
b. R = CH_2Ph
c. R = Ph



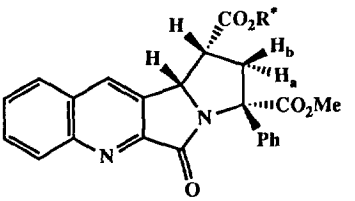
(14)



(15) a. R = Me
b. R = CH_2Ph
c. R = Ph



(16)



(17)

One pot combination cascades were next explored using thermal 1,2-prototropy to generate the 1,3-dipole. These reactions were carried out in boiling toluene and the imine → azomethine ylide → cycloadduct cascade was allowed to precede for 24h before addition of the palladium catalyst and TlOAc. The second carbonylation-cyclisation cascade was complete after a further 48h. In this way the products (7a)(60%), (7d)(66%), and (8)(58%) were obtained.

Experimental. General experimental details were as previously described.[13]

General Procedure for Thermal Cycloaddition. A solution of the aldehyde (0.2mmol), α-amino ester (0.2mmol) and N-methylmaleimide (0.2mmol) in dry toluene (50ml) was boiled under reflux for 24h. The solvent was then evaporated under reduced pressure and the residue either crystallised from methanol or purified by flash chromatography over silica as appropriate.

Methyl 2-benzyl-4-(2'1-iodophenyl)-7-methyl-6,8-dioxo-1,7-diazabicyclo[3.3.0]octane-2-carboxylate(6a). The crude cycloadduct was directly crystallised from methanol to afford the **product** (75%) as colourless prisms, m.p. 154-156°C (Found: C, 52.65; H, 4.15; N, 5.65. $C_{22}H_{21}IN_2O_4$ requires C, 52.4; H, 4.15; N, 5.55%); δ 7.9-7.0(m, 9H, ArH), 5.0(dd, 1H, 4-H), 4.0(s + t, 4H, OMe and 5-H), 3.6 and 3.2(2xd, 2H, $PhCH_2$), 3.4(d, 1H, 1-H), 2.8(s, 3H, NMe) and 2.2(br s, 1H, NH); m/z(%) 504(M^+,0.2), 445(54), 413(100), 302(17), 141(10), 115(10), 91(36) and 77(5).

Methyl 2-phenyl-4-(2′-iodophenyl)-7-methyl-6,8-dioxo-1,7-dizabicyclo[3.3.0]octane-2-carboxylate (6b). The crude cycloadduct was directly crystallised from methanol to afford the **product** (70%) as colourless prisms, m.p. 230-232°C (Found: C, 51.1; H, 3.75; N, 5.75. $C_{21}H_{19}IN_2O_4$ requires C, 51.4; H, 3.85; N, 5.7%); δ 7.9-7.0(m, 9H, ArH), 4.4(br d, 1H, 4-H), 4.1(d, 1H, 1-H), 4.0(s, 3H, OMe), 3.8(t, 1H, 5-H), 3.0(br s, 1H, NH) and 2.8(s, 3H, NMe); m/z(%) 490(M^+,1.5), 431(100), 379(28), 319(35), 193(21), 152(11), 115(19) and 77(10).

Methyl 2-benzyl-4-(2′-iodopyrid-3′-yl)-7-methyl-6,8-dioxo-1,7-diazabicyclo[3.3.0]octane-2-carboxylate (6c). The crude cycloadduct was purified by flash chromatography eluting with 1:1v/v ethyl acetate-petroleum ether to afford the product (80%) which crystallised from ether-petroleum ether as colourless prisms, m.p. 165-167°C (Found: C, 50.05; H, 3.75; N, 8.2; I, 25.3. $C_{21}H_{20}IN_3O_4$ requires C, 49.9; H, 4.0; N, 8.3; I, 25.1%): δ 8.25-7.10(m, 8H, ArH), 4.92(dd, 1H, J8.7 and 3.1Hz, 4-H), 3.9(t, 1H, J8.4Hz, 5-H), 3.81(s, 3H, OMe), 3.62 and 3.1(2xd, 2x1H, J13.8Hz, $PhCH_2$), 3.42(d, 1H, J7.8Hz, 1-H), 2.91(s, 3H, NMe) and 2.18(br, 1H, NH) m/z(%) 505(M^+,3), 446(14), 414(100), 382(13), 201(18), 176(15) and 91(66).

Methyl 2-phenyl-4-(4′-iodo-N-phenylsulphonylindol-3′-yl)-7-methyl-6,8-dioxo-1,7-diazabicyclo[3.3.0]octane-2-carboxylate (6d). The crude cycloadduct was directly crystallised from methanol to afford the **product** (72%) as colourless prisms, m.p. 222-224°C (Found: C, 51.75; H, 3.3; N, 6.7. $C_{29}H_{24}IN_3O_6$ requires C, 52.0; H, 3.6; N, 6.25%); δ 8.0-7.0(m, 14H, ArH), 5.0(dd, 1H, 4-H), 4.05(d, 1H, 1-H), 3.83(s, 3H, OMe), 3.89(t, 1H, 5-H), 2.9(br s, 1H, NH) and 2.8(s, 3H, NMe); m/z(%) 669(M^+,3), 610(60), 558(45), 469(11), 417(33), 231(28), 106(100), 91(53) and 77(44).

Methyl 2-benzyl-4-(2′iodoquinolin-3′-yl)-7-methyl-6,8-dioxo-1,7-diazabicyclo[3.3.0]octane-2-carboxylate (6e). The crude cycloadduct was purified by flash chromatography eluting with 1:2 v/v ethyl acetate-petroleum ether to afford the **product** (85)% which crystallised from ether-petroleum ether as colourless prisms, m.p. 254-255°C (Found: C, 54.15; H, 4.0, N, 7.35; I, 22.8. $C_{25}H_{22}IN_3O_4$ requires C, 54.05; H, 4.0; N, 7.55; I, 22.85%); δ8.04-7.10(m, 10H, ArH), 5.08(dd, 1H, J8.9 and 3.0Hz, 4-H), 4.09(t, 1H, J8.3Hz, 5-H), 3.94(s, 3H, OMe), 3.60 and 3.15(2xd, 2H, J13.7Hz, $PhCH_2$), 3.49(d, 1H, J7.7Hz, 1-H), 2.71(s, 3H, NMe) and 2.26(br, 1H, NH); m/z(%) 555(M^+,2), 496(35), 464(100), 372(21) and 91(31).

General Procedure for the Preparation of Imines. A mixture of the α-amino ester hydrochloride (1.1 equiv), anhydrous magnesium sulphate (4 equiv) and triethylamine (1.2 equiv) in dry dichloromethane was stirred for 15 min before addition of the appropriate aldehyde (1 equiv). The resulting mixture was stirred at room temperature for 12h and then filtered. The filtrate was washed with water, dried ($MgSO_4$) and evaporated. The residual crude imine was used directly for the next stage without further purification except for imine (10g).

Methyl N-(2-iodobenzylidene)-alaninate (10a). The crude imine (89%) was a pale yellow gum. δ 8.5(s, 1H, HC=N), 7.12-8.06(m, 4H, ArH), 4.27(q, 1H, C<u>H</u>Me), 3.78(s, 3H, OMe) and 1.58(d, 3H, J6.8Hz, CH<u>Me</u>); m/z(%) 317(M^+,32), 302(24), 258(100), 130(83), 104(47), 88(86) and 76(30).

Methyl N-(2-iodobenzylidene)-phenylalaninate (10b). The crude imine (88%) was a pale yellow gum. δ 8.5(s, 1H, HC=N), 7.0-7.96(m, 9H, ArH), 4.26(dd, 1H, J9.2 and 4.7Hz, C<u>H</u>CH_2) 3.71(s, 3H, OMe), 3.31(dd, 1H, J13.5 and 4.8Hz, PhC<u>H</u>) and 3.12(dd, 1H, J13.9 and 9.3Hz, PhCH); m/z(%) 393(M^+,23), 333(38), 302(100), 242(34) and 91(43).

Methyl N-(2-iodobenzylidene)-phenylglycinate (10c). The crude imine (91%) was a thick pale yellow oil. δ 8.51 (s, 1H, HC=N), 7.1-7.82(m, 9H, ArH), 5.28(s, 1H, NCH) and 3.75(s, 3H, OMe); m/z(%) 379(M^+,9), 320(100), 193(40), 165(26), 150(11) and 90(17).

Methyl N-(4-iodo-N-phenylsulponylindolyl-3-methylidene)-alaninate (10d). The crude imine (90%) was a pale brown solid, m.p. 115-118°C. δ 9.41(s, 1H, HC=N), 8.2-6.91 (m, 9H, ArH and indole 2-H), 4.22(q, 1H,

J6.7hz, CHMe), 3.76(s, 3H, OMe) and 1.53(d, 3H, CHMe); m/z(%) 496(M^+,30), 437(100), 409(17), 296(38), 169(25) and 128(31).

Methyl N-(4-iodo-N-phenylsulphonylindolyl-3-methylidene)-phenylalaninate (10e). The crude imine (88%) was obtained as a pale red-brown gum. δ 9.01(s, 1H, HC=N), 8.21-6.90(m, 14H, ArH and indole 2-H), 4.21(dd, J9.3 and 4.8Hz, $CHCH_2$), 3.76(s, 3H, OMe), 3.31(dd, 1H, J13.2 and 4.9Hz, PhCH) and 3.1(dd, J13.2 and 9.2Hz, PhCH); m/z(%) 572(M^+,11), 481(97), 341(34), 254(28), 91(96) and 77(100).

Methyl N-(4-iodo-N-phenylsulphonylindolyl-3-methylidene)-phenylglycinate (10f). The crude imine (89%) was obtained as a pale red-brown gum. δ 9.43(s, 1H, HC=N), 8.31-6.96(m, 14H, ArH and indole 2-H), 5.29(s, 1H, PhCH) and 3.76(s, 3H, OMe); m/z(%) 558(M^+,13), 499(97), 358(36), 231(29), 104(23) and 77(100).

Methyl N-(2-iodoquinolinyl-3-methylidene)-phenylglycinate (10g). Crystallisation of the crude imine from ether-petroleum ether afforded the **product** (92%) as colourless prisms, m.p. 126-128 °C (Found: C, 53.15; H, 3.35; N, 6.45; I, 29.7. $C_{19}H_{15}IN_2O_2$ requires C, 53.05; H, 3.5; N, 6.5; I, 29.5%); δ 8.63(s, 1H, HC=N), 8.6(s, 1H, quinoline 4-H), 7.93-7.30(m, 9H, ArH), 5.39(s, 1H, PhCH) and 3.75(s, 3H, OMe); m/z(%) 430(M^+,7), 372(20), 371(100), 279(38) and 216(35).

General Procedure for the Metal Catalysed Cycloaddition Reactions. A mixture of the imine (1 equiv), DBU or 2-t-butyl-1,1,3,3-tetramethylguanidine (1.1 equiv), (1S, 2R, 5S)-menthyl acrylate (1 equiv) and silver acetate or lithium bromide (1.5 equiv) in freshly distilled acetonitrile was stirred at room temperature for the appropriate time (Table 2). The reaction was then quenched by addition of saturated aqueous ammonium chloride solution, and extracted with methylene chloride (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by flash chromatography over silica to afford the cycloadduct. The yields are collected in Table 2.

1S, 2R, 5S-Menthyl-r-2S-methoxycarbonyl-2-methyl-c-5S-(2′-iodophenyl)pyrrolidine-c-4R-carboxylate (11a). After flash chromatography eluting with 2:1v/v petroleum ether-ether the **product** was obtained as a pale yellow gum. (Found: C, 54.55; H, 6.55; N, 2.8; I, 23.75. $C_{24}H_{34}INO_4$ requires C, 54.65; H, 6.5; N, 2.65; I, 24.05%); $[\alpha]_D$-52.5 (c.1g/100ml, EtOH); δ 7.78-6.93(m, 4H, ArH), 4.70(d, 1H, J7.5Hz, 5-H), 4.25(m, 1H, OCH), 3.82(s, 3H, OMe), 3.65(m, 1H, 4-H), 2.90(br, 1H, NH), 2.75(dd, 1H, J11.6 and 1.8Hz, 3-Ha), 2.08(dd, 1H, J11.6 and 7.4Hz, 3-Hb) 1.70(m, 1H, menthyl-H), 1.50(s, 3H, 2-Me), 1.49(m, 1H, menthyl-H), 1.10-1.32(m, 2H, menthyl-H), 0.84(d, 3H, 6.9Hz, Me), 0.86(m, 4H, menthyl-H), 0.54, 0.69(2xd, 6H, J6.7Hz, $CHMe_2$) and -0.03(m, 1H menthyl-H); m/z(%) 528(M+1,9), 489(12), 468(100), 330(59), 317(55), 257(77), 86(45) and 84(66).

1S, 2R, 5S-Menthyl 2S-benzyl-r-2-methoxycarbonyl-c-5S-(2′-iodophenyl)pyrrolidine-c-4R-carboxylate (11b). After flash chromatography eluting with 2:1v/v petroleum ether-ether the **product** crystallised from ether-petroleum ether as colourless prisms, m.p. 88-90 °C (Found: C, 59.7; H, 6.55; N, 2.5; I, 20.8. $C_{30}H_{38}INO_4$ requires C, 59.7; H, 6.35; N, 2.3; I, 21.0%); [α]-12.3 (c. 0.65g/100gm, EtOH); δ 7.70-6.93(m, 9H, ArH), 4.70(d, 1H, J7.9Hz, 5-H), 4.21(m, 1H, OCH), 3.72(s, 3H, OMe), 3.50(m, 1H, 4-H), 2.91 and 3.10(2xd, 2H, J13.2Hz, CH_2Pd), 2.77(dd, 1H, J13.6 and 4.4Hz, 3-Ha), 2.69(br, 1H, NH), 2.20(dd, 1H, J13.6 and 8.1Hz, 3-Hb) 1.70(m, 1H, menthyl-H), 1.52 (and 1.11(2xm, 2x2H, menthyl-H), 0.81(d, 3H, J7.0Hz, Me), 0.68(m, 3H, menthyl-H), 0.62, 0.66(2xd, 6H, J6.8Hz, $CHMe_2$) and -0.04(m, 1H, menthyl-H); m/z(%) 604(M+1,10), 545(15), 512(100), 374(89), 91(36), and 55(17).

1S, 2R, 5S-Menthyl r-2S-methoxycarbonyl-2-phenyl-c-5S-(2′-iodophenyl)pyrrolidine-c-4R-carboxylate (11c). After flash chromatography eluting with 2:1 v/v petroleum ether-ether the **product** crystallised from ether-petroleum ether as pale yellow prisms, m.p. 34-37 °C (Found: C, 59.1; H, 6.25; N, 2.2; I, 21.35. $C_{29}H_{36}INO_4$ requires C, 59.1; H, 6.15; N, 2.4; I, 21.5%); $[\alpha]_D$ - 25.7 (c.1g/100ml, EtOH); δ 7.78-6.90(m, 9H,

ArH), 4.60(d, 1H, J7.6Hz, 5-H), 4.21(m, 1H, OCH), 3.70(s, 3H, OMe), 3.50(m, 1H, 4-H), 3.40(br, 1H, NH), 3.10(dd, 1H, J13.0 and 5.4Hz, 3-Ha), 2.60(dd, 1H, J13.1 and 7.6Hz, 3-Hb), 1.70(m, 1H, menthyl-H), 1.50 and 1.15(2xm, 2x2H, menthyl-H), 0.79(d, 3H, J7.0Hz, Me), 0.80(m, 3H, menthyl-H), 0.61, 0.68(2xd, 6H, J6.9Hz, CH$\underline{Me}_2$) and 0.02(m, 1H, menthyl-H); m/z(%) 590(M+1,13), 531(72), 530(100), 392(76), 220(42), and 55(32).

1S, 2R, 5S-Menthyl r-2S-methoxycarbonyl-2-methyl-c-5S-(4′-iodo-N-phenylsulphonylindol-3′-yl) pyrrolidine-c-4R-carboxylate (11d). After flash chromatography eluting with 1:1 v/v petroleum ether-ether the **product** crystallised from ether-petroleum ether as colourless prisms, m.p. 58-61 °C (Found: C, 54.15; H, 5.6; N, 4.25; I, 17.9; S, 4.6. $C_{32}H_{39}IN_2O_6S$ requires C, 54.4; H, 5.55; N, 3.95; I, 17.95; S, 4.55%); $[\alpha]_D$-51.0 (c. 0.77g/100ml, EtOH); δ 7.91-6.93(m, 9H, ArH and indole 2-H), 5.56(d, 1H, J7.9Hz, 5-H), 4.18(m, 1H, OCH), 3.85(s, 3H, OMe), 3.70(m, 1H, 4-H), 2.81(dd, 1H, J13.3 and 5.0Hz, 3-Ha), 2.10(dd, 1H, J13.3 and 7.9Hz, 3-Hb) 1.70(m, 1H, menthyl-H), 1.53(s, 3H, 2-Me), 1.41(m, 2H, menthyl-H), 1.25(m 1H, menthyl-H), 0.90(m, 4H, menthyl-H), 0.75(d, 3H, J7.8Hz, Me), 0.41, 0.62(2xd, 6H, J6.8Hz, CH$\underline{Me}_2$) and -0.03(m, 1H, menthyl-H); m/z(%) 707(M+1,6), 647(94), 496(100), 355(74), 169(20), 83(37), and 77(55).

1S, 2R, 5S-Menthyl 2S-benzyl-r-2-methoxycarbonyl-c-5S-(4′-iodo-N-phenylsulphonylindol-3′-yl)pyrrolidine-c-4R-carboxylate (11e). After flash chromatography eluting with 1:1 v/v petroleum ether-ether, the **product** crystallised from ether-petroleum ether as pale yellow prisms, m.p. 52-55 °C (Found: C, 58.2; H, 5.4; N, 3.3; I. 16.05; S, 4.25. $C_{38}H_{43}IN_2O_6S$ requires C, 58.3; H, 5.5; N, 3.55; I, 16.2; S; 4.1%); $[\alpha]_D$-14.0 (c.1g/100ml, EtOH); δ 7.91-6.90(m, 14H, ArH and indole 2-H), 5.60(d, 1H, J8.3Hz, 5-H), 4.20(m, 1H, OCH), 3.70(s, 3H, OMe), 3.62(m, 1H, 4-H), 3.00 and 3.22(2xd, 2H, J13.3Hz, CH_2Ph) 2.80(dd, 1H, J13.1 and 5.1Hz, 3-Ha), 2.30(dd, 1H, J13.1 and 7.9Hz, 3-Hb) 1.70(m, 1H, menthyl-H), 1.63 and 1.45(2xm, 2x2H, menthyl-H), 0.91(m, 3H, menthyl-H), 0.80(d, 3H, J6.5Hz, Me), 0.41, 0.60(2xd, 6H, J6.9Hz, CH$\underline{Me}_2$) and -0.5(m, 1H, menthyl-H); m/z(%) 784(M^+, 100), 645(21), 91(17), and 83(42).

1S, 2R, 5S-Menthyl r-2S-methoxycarbonyl-2-phenyl-c-5S-(4′-iodo-N-phenylsulphonylindol-3′-yl)pyrrolidine-c-4R-carboxylate (11f). After flash chromatography eluting with 1:1 v/v petroleum ether-ether the **product** crystallised from ether-petroleum ether as colourless prisms, m.p. 68-71 °C (Found: C, 58.05; H, 5.5; N, 3.5; I, 16.4; S, 4.15. $C_{37}H_{41}IN_2O_6S$ requires C, 57.8; H, 5.35; N, 3.65; I, 16.5; S, 4.15%); $[\alpha]_D$-30.8 (c 1g/100ml, EtOH); δ 7.90-6.90(m, 14H, ArH and indole 2-H), 5.40(d, 1H, J8.2Hz, 5-H), 4.12(m, 1H, OCH), 3.77(s, 3H, OMe), 3.62(m, 1H, 4-H), 3.10(dd, 1H, J13.3 and 6.5Hz, 3-Ha), 2.77(dd, 1H, J13.3 and 7.7Hz, 3-Hb) 1.70 and 1.43(2xm, 2x2H, menthyl-H), 0.75(d, 3H, J6.9Hz, Me), 0.42, 0.64(2xd, 6H, J7.0Hz, CH$\underline{Me}_2$) and -0.5(m, 1H, menthyl-H); m/z(%) 769(M+1,67), 709(39), 571(13), 144(14), 83(69) and 55(100).

1S, 2R, 5S-Menthyl r-2S-methoxycarbonyl-2-phenyl-c-5S-(2′-iodoquinolin-3-yl)pyrrolidine-c-4R-carboxylate (11g). After flash chromatography eluting with 3:2 v/v petroleum ether-ether the **product** crystallised from ether-petroleum ether as colourless prisms, m.p. 70-73 °C. (Found: C, 60.15; H, 6.0; N, 4.3; I, 19.8. $C_{32}H_{37}IN_2O_4$ requires C, 60.0; H, 5.8; N, 4.3; I, 19.8%); [α] + 37.6 (c. 1g/100ml, EtOH); δ 8.22-7.26(m, 10H, ArH), 4.75(d, 1H, J7.8Hz, 5-H), 4.16(m, 1H, OCH), 3.79(s, 3H, OMe), 3.73(m, 1H, 4-H), 3.40(br, 1H, NH), 3.28(dd, 1H, J13.8Hz and 4.3Hz, 3-Ha), 2.76(dd, 1H, J13.7 and 7.8Hz 3-Hb), 1.70(m, 1H, menthyl-H) 1.41-1.05(m, 3H, menthyl-H), 0.92(m, 2H, menthyl-H) 0.80, 0.63(2xd, 6H, J7.0Hz, CH$\underline{Me}_2$), 0.31(m,2H, menthyl-H), 0.07(d, 3H, J6.5Hz, Me) and -0.64(m, 1H, menthyl-H); m/z(%) 640(M^+,42), 582(27), 581(100), 443(59), 315(40) and 271(45).

General Procedure for Carbonylation Reactions. Cycloadduct (1mmol), $Pd(OAc)_2$ (22mg, 0.1mmol), PPh_3(56mg, 0.2mmol) and TlOAc (709mg, 3mmol) were mixed in dry acetonitrile (30ml) in a 100ml round bottomed flask equipped with a reflux condenser. A carbon monoxide filled balloon was attached to the top of the condenser and the mixture was stirred and boiled under reflux for 2-2.5 dy. The reaction mixture was

then cooled, filtered to remove inorganic salts and solvent removed under reduced pressure. The residue was partitioned between water (25ml) and methylene chloride (30ml), the organic layer separated and the water layer extracted with a further portion of methylene chloride. The combined organic layers were dried (anhy. Na_2SO_4) and the solvent removed. The residue was crystallised from MeOH or purified by flash chromatography over silica as appropriate. Product yields are collected in Tables 1 and 2.

Lactam (7a). The crude material was directly crystallised from methanol to afford the **product** as colourless plates, m.p. 224-226 °C (Found: C, 68.0; H, 5.25; N, 6.8. $C_{23}H_{20}N_2O_5$ requires C, 68.31; H, 4.95; N, 6.93%); δ 7.8-6.9(m, 9H, ArH), 4.2(d, 1H, 4-H), 4.0(d, 1H, 1-H), 3.7(d, 1H, PhCH), 3.62(s, 3H, OMe), 3.4(d, 1H, PhCH), 3.3(t, 1H, 5-H) and 2.8(s, 3H, NMe); m/z(%) 404(M^+,9), 345(10), 313(100), 228(27), 184(14), 169(22), 91(20) and 59(11).

Lactam (7b). The crude material was directly crystallised from methanol to afford the **product** as colourless prisms, m.p. 278-280 °C (Found: C, 64.5; H, 4.5; N, 7.2. $C_{22}H_{18}N_2O_5$ requires C, 64.7; N, 4.45; N, 6.85%); δ 7.8-7.38(m, 9H, ArH), 5.31 (d, 1H, J8.25Hz, 4-H), 4.26(d, 1H, J8.7Hz, 1-H), 3.74(t, 1H, J8.3Hz, 5-H), 3.65(s, 3H, OMe) and 2.9(s, 3H, NMe); m/z(%) 390(M^+,0.3), 331(100), 246(50), 217(10), 165(5) and 57(40).

Lactam (7c). After flash chromatography eluting with 1:1v/v ethyl acetate-petroleum ether followed by crystallisation from ether-petroleum ether the **product** was obtained as colourless prisms, m.p. 250-253 °C (Found: C, 65.05; H, 4.65; N, 10.25. $C_{22}H_{19}N_3O_5$ requires C, 65.15; H, 4.7; N, 10.35%); δ 8.76-7.30(m, 8H, ArH), 4.15(d, 1H, J8.8Hz, 4-H), 3.97(d, 1H, 8.3Hz, 1-H), 3.78 and 3.42(2xd, 2H, J14.1Hz, $PhCH_2$), 3.68(s, 3H, OMe), 3.34(t, 1H, J.8.6Hz, 5-H) and 2.80(s, 3H, NMe); m/z(%) 405(M^+,13), 346(18), 330(10), 314(100) and 229(10).

Lactam (8). The crude material was directly crystallised from methanol to afford the **product** as colourless prisms, m.p. 270 °C(d) (Found: C, 63.1; H, 3.9; N, 7.35. $C_{30}H_{23}N_3O_7S$ requires C, 63.26; H, 4.04; N, 7.38%); δ 8.0-7.0(m, 14H, ArH), 5.56(d, 1H, 4-H), 3.85(d, 1H, 1-H), 3.8(t, 1H, 5-H), 3.6(s, 3H, OMe) and 2.9(s, 3H, NMe); m/z(%) 569(M^+,0.5), 510(2), 413(35), 359(20), 247(35), 218(22), 167(11), 149(28), 141(13), 125(19), 91(39), 55(40) and 32(100).

Lactam (9). After purification by chromatography on neutral alumina eluting with 1:1 v/v petroleum ether-ethyl acetate and crystallisation from ether-petroleum ether the **product** was obtained as colourless prisms, m.p. 275-277 °C (Found: C, 68.5; H, 4.5; N, 9.1. $C_{26}H_{21}N_3O_5$ requires C, 68.55; H, 4.65; N, 9.2%); δ 8.40-7.27(m, 10H, ArH), 4.27(d, 1H, J8.8Hz, 4-H), 4.02(d, 1H, J8.4Hz, 1-H), 3.87 and 3.48(2xd, 2H, J13.7Hz, $PhCH_2$), 3.69(s, 3H, OMe), 3.42(t, 1H, J8.7Hz, 5-H) and 2.79 (s, 3H, NMe); m/z(%) 455(M^+,47), 396(49), 364(100), 344(31) and 91(33).

Lactam (13a). Prepared from (11a) by the general procedure and purified by chromatography on neutral alumina eluting with 4:1 v/v petroleum ether-ethyl acetate. The **product** crystallised from ether-petroleum ether as a pale yellow prisms, m.p. 109-111 °C (Found: C, 70.35; H, 7.85; N, 3.4. $C_{25}H_{33}NO_5$ requires C, 70.25; H, 7.75; N, 3.25%); $[\alpha]_D$ - 20.0 (c.1g/100ml, EtOH); δ 7.30-7.61(m, 4H, ArH), 5.03(d, 1H, J7.0Hz, 5-H), 4.32(m, 1H, OCH), 3.57(s, 3H, OMe), 3.28(t, 1H, J7.4Hz,4-H), 3.15(d, 1H, J13.9Hz, 3-Ha), 2.36(dd, 1H, J13.9 and 7.9Hz, 3-Hb), 1.62(s, 3H, 2-Me), 1.40(m, 4H, menthyl-H), 1.12(m, 1H, menthyl-H), 0.80(m, 3H, menthyl-H) 0.72(d, 3H, J7.0Hz, Me), 0.50 and 0.59(2xd, 6H, J6.6Hz, $CH\underline{Me}_2$) and -0.01(m, 1H, menthyl-H); m/z(%) 427(M^+,6), 368(47), 230(100), 184(18) and 84(66).

Lactam (13b). Prepared from (11b) by the general procedure and purified by chromatography on neutral alumina eluting with 4:1 v/v petroleum ether-ether acetate. The **product** crystallised from ether-petroleum ether as a pale yellow prisms, m.p. 147-149 °C (Found: C, 73.8; H, 7.4; N, 2.9. $C_{31}H_{37}NO_5$ requires: C,73.9; H,7.4: N,2.8%); $[\alpha]_D$-12.3 (c. 0.65g/100ml, EtOH); δ 7.90-7.21(m, 9H, ArH), 4.40(m, 1H, OCH), 4.23(d, 1H, J6.9Hz,

5-H), 3.77(s, 3H, OMe), 3.30 and 3.72(2xd, 2H, J13.1Hz, $PhCH_2$), 3.10(m, 2H, 4-H and 3-Ha), 2.70(dd, 1H, J13.8 and 7.8Hz, 3-Hb), 1.40-1.72(m, 5H, menthyl-H), 1.20(m, 1H, menthyl-H), 0.97(m, 2H, menthyl-H), 0.87(d, 3H, J7.1Hz, Me), 0.67 and 0.73(2xd, 6H, J6.5Hz, $CH\underline{Me}_2$) and -0.01(m, 1H, menthyl-H); m/z(%) 503(M^+,4), 444(19), 413(48), 412(100), 306(47), 274(92) and 132(60).

Lactam (13c). Prepared from (11c) by the general procedure and purified by chromatography on neutral alumina eluting with 4:1 v/v petroleum ether-ethyl acetate. The **product** crystallised from ether-petroleum ether as a colourless prism, m.p. 50-53 °C (Found: C, 73.5; H, 7.4; N, 2.8. $C_{30}H_{35}NO_5$ requires C, 73.6; H, 7.2; N, 2.85%); $[\alpha]_D$-110.4C (c. 1g/100ml, EtOH); δ 7.87-7.31(m, 9H, ArH), 5.13(d, 1H, J7.7Hz 5-H), 4.50(m, 1H, OCH), 3.69(s, 3H, OMe), 3.70(dd, 1H, J13.1Hz and 3.3Hz, 3-Ha), 3.37(m, 1H, 3-H), 2.98(dd, 1H, J13.1 and 8.0Hz, 3-Hb), 1.62(m, 3H, menthyl-H), 1.35(m, 2H, menthyl-H), 0.95(m, 3H, menthyl-H), 0.86(d, 3H, J6.3Hz, Me), 0.64 and 0.80(2xd, 6H, J6.1Hz, $CH\underline{Me}_2$) and -0.3(m, 1H, menthyl-H); m/z(%) 489(M^+,10), 430(77) 292(100), 115(14), and 55(15).

Lactam (15a). Prepared from (11d) by the general procedure and purified by chromatography on neutral alumina eluting with 4:1 v/v petroleum ether-ethyl acetate. The **product** crystallised from ether-petroleum ether as pale yellow prisms, m.p. 80-83 °C (Found: C, 65.4; H, 6.25; N, 4.7; S, 5.4. $C_{33}H_{38}N_2O_7S$ requires C, 65.3; H, 6.3; N, 4.6; S, 5.3%); $[\alpha]_D$-57.6 (c. 1g/100ml, EtOH); δ 8.02-7.21(m, 9H, ArH and indole 2′-H), 5.31(d, 1H, J.64Hz, 5-H), 4.36(m, 1H, OCH), 3.69(s, 3H, OMe), 3.53(t, 1H, J7.6Hz 4-H), 2.75(d, 1H, J13.8Hz, 3-Ha), 2.23(dd, 1H, J13.8 and 8.9Hz, 3-Hb) 1.81(m, 1H, menthyl-H), 1.69(s, 3H, 2-Me), 1.21-1.58(m, 5H, menthyl-H), 0.81(d, 3H, J6.5Hz, Me), 0.61(m, 3H, menthyl-H) and 0.52 and 0.01 (2xd, 2x3H, J6.8Hz, $CH\underline{Me}_2$); m/z(%) 606(M^+,21), 547(79), 464(39), 327(43), 277(97), 223(100) and 183(22).

Lactam (15b). Prepared from (11e) by the general procedure and purified by chromatography on neutral alumina eluting with 4:1 v/v petroleum ether-ethyl acetate. The **product** crystallised from ether-petroleum ether as pale yellow prisms, m.p. 95-98 °. (Found: C, 68.75; H, 6.5; N, 4.1; S, 4.9. $C_{39}H_{42}N_2O_7S$ requires: C, 68.6; H, 6.2; N, 4.1; S, 4.7%); $[\alpha]_D$-75.2 (c. 1g/100ml, EtOH); δ 8.00-7.18(m, 14H, ArH and indole 2′-H), 4.39(m, 1H, OCH), 4.02(d, 1H, J6.5Hz, 5-H), 3.15 and 4.05(2xd, 2H, J13.3Hz, CH_2Ph), 3.72(s, 3H, OMe), 3.12(m, 1H, 4-H), 2.69(m, 2H, 3-Ha and 3-Hb), 1.71(m, 1H, menthyl-H), 1.52, 1.30 and 0.95(3xm, 3x2H, menthyl-H), 0.78(d, 3H, J6.5Hz, Me), 0.61(d, 3H, J6.9Hz, Me), 0.52(m, 2H, menthyl-H) and 0.22(d, 3H, J6.8Hz, Me); m/z(%) 683(M+1,6), 591(25), 541(82), 453(55), 403(100), 359(40), 311(26) and 83(42).

Lactam (15c). Prepared from (11f) by the general procedure and purified by chromatography on neutral alumina eluting with 4:1 v/v petroleum ether-ethyl acetate. The **product** crystallised from ether-petroleum ether as pale yellow prisms, m.p. 113-116 °C. (Found: C, 68.3; H, 6.2; N, 3.9; S, 4.95. $C_{38}H_{40}N_2O_7S$ requires: C, 68.25; H, 6.0; N, 4.2; S, 4.8%); $[\alpha]_D$-72.8 (c. 1g/100ml, EtOH); δ 8.05-7.20(m, 14H, ArH and indole 2′-H), 5.21(d, 1H, J6.6Hz, 5-H), 4.35(m, 1H, OCH), 3.70(s, 3H, OMe), 4.49(m, 1H, 4-H), 3.24(dd, 1H, J13.5 and 2.5Hz, 3-Ha), 2.8(dd, 1H, J13.5 and 9.1Hz; 3-Hb), 1.91(m, 1H, menthyl-H), 1.62, 1.50 and 1.05(3xm, 3x2H, menthyl-H), 0.83(d, 3H, J6.5Hz, Me), 0.62(m, 2H, menthyl-H), 0.54(d, 3H, J7.0Hz, Me) and -0.01(d, 3H, J6.6Hz, Me); m/z(%) 669(M+1,23), 668(44), 609(52), 528(53), 527(100), 471(54), 389(46), 329(50), 285(72) and 125(19).

Lactam (17). Prepared from (11g) by the general procedure and purified by chromatography on neutral alumina eluting with 4:1 v/v petroleum ether-ethyl acetate. The **product** crystallised from ether-petroleum ether as colourless prisms, m.p. 220-222 °C (Found: C, 73.2; H, 6.75; N, 5.1. $C_{33}H_{36}N_2O_5$ requires C, 73.3; H, 6.7; N, 5.2%); $[\alpha]_D$ + 236.8 (c. 0.9g/100ml, $CHCl_3$); δ 8.41-7.26(m, 10H, ArH), 5.26(d, 1H, J7.4Hz, 5H), 4.41(m, 1H, OCH), 3.74(dd, 1H, J13.9 and 3.3Hz, 3-Ha), 3.71(s, 3H, OMe), 3.53(m, 1H, 4-H), 3.07(dd, 1H, J13.8 and 8.0Hz, 3-Hb), 1.42(m, 3H, menthyl-H), 1.20(m, 2H, menthyl-H), 0.80 (m, 3H, menthyl-H), 0.67 and 0.49 (2xd,

6H, J7.0Hz, $CH\underline{Me}_2$), 0.58(d, 3H, J6.5Hz, Me) and 0.14(m, 1H, menthyl-H); m/z(%) 540(M^+,2), 482(46), 481(99), 479(23), 343(100) and 297(30).

Reduction of Lactams.

Diol (14). Lactam (13c) (0.28g, 0.57mmol) in dry ether (10ml) was added dropwise to stirred solution of $LiAlH_4$(0.08g, 2.2mmol) in dry ether. The reaction mixture was boiled under reflux for 8h., cooled and unreacted hydride destroyed by careful dropwise addition of water. The white precipitate was filtered and washed with ether. The combined filtrates were dried ($MgSO_4$) and evaporated and the residue was crystallised from ether-petroleum ether to afford the **product** (0.11g, 66%) as colourless prisms, m.p. 59-62 °C (found: C, 77.35; H, 7.35; N, 4.6. $C_{19}H_{21}NO_2$ requires C, 77.25; H, 7.15; N, 4.75%); $[\alpha]_D$-22.4 (c. 1g/100ml, EtOH); δ 7.71-7.19(m, 9H, ArH), 4.56(d, 1H, J7.5Hz, 5-H), 4.37(s, 2H, 2-CH_2O), 4.01 and 3.87 (2xd, 2H, J11.7Hz, NCH_2), 3.41 and 3.22 (2xdd, 2H, J11.2 and 5.6Hz, 4-CH_2O), 2.45(dd, 1H, J12.5 and 7.49Hz, 3-Hb), 2.31(m, 1H, 4-H), 1.87(dd, 1H, J12.5 and 10.2Hz, 3-Ha) and 1.6(br, 2H, 2xOH); m/z(%) 295(M^+,2), 293(11), 264(100), 244(49), 230(27) and 130(37).

Diol (16). Lactam (15c) (0.3g, 0.44mmol) in dry ether (10ml) was added dropwise to stirred solution of $LiAlH_4$(0.08g, 2.2mmol) in dry ether. The reaction mixture was refluxed for 8h then cooled, and unreacted hydride was quenched by dropwise addition of water. The white precipitate was filtered and washed with ether. The filtrate was dried ($MgSO_4$), and evaporated and the residue was crystallised from ether-petroleum ether to afford the **product** (0.09g, 60%) as a pale yellow powder, m.p. 108-111 °C. Accurate mass: 334.1668. $C_{21}H_{22}N_2O_2$ requires: 334.1681. $[\alpha]_D$-32.1 (c.0.81g/100ml, EtOH); δ ($CDCl_3$ + 3 drops TFA) 7.56-6.83(m, 9H, ArH and indole 2'-H), 5.06(d, 1H, J6.3Hz, 5-H), 5.01 and 4.23(2xd, 2H, J13.1Hz, 4-CH_2O), 4.71 and 3.78(2xd, 2H, J13.3Hz, 2-CH_2O), 4.51 and 4.10(2xd, 2H, J12.6Hz, NCH_2), 3.41(m, 1H, 4-H), 3.23(dd, 1H, J13.1 and 7.2Hz, 3-Hb), 2.92(dd, 1H, J13.1 and 4Hz, 3-Ha); m/z(%) 334(M^+,8), 304(74), 303(100), 287(21), 284(43), 271(31), 245(29), 183(12) and 152(19).

General Procedure for One-pot Cycloaddition-Carbonylation Reactions. A solution of the appropriate imine (1mmol) and N-methylmaleimide (1mmol) in dry toluene (25ml) was boiled under reflux for 24h. $Pd(OAc)_2$ (22mg, 0.1mmol), PPh_3(56mg, 0.2mmol) and TlOAc (312mg, 1.2mmol) were then added to the hot solution and a balloon filled with carbon monoxide was attached to the top of the condenser. The mixture was stirred and heated at 100 °C for 2 dy. The mixture was then cooled and filtered to remove inorganic salts. The solvent was evaporated and the residue partitioned between water (25ml) and methylene chloride (30ml). The organic layer was separated, dried (anhy. Na_2SO_4) and evaporated. The residue was crystallised from methanol to afford the pure lactam.

Lactam (7a). Obtained in 60% yield, m.p. 224-226 °C. The spectroscopic data were identical to those described above.

Lactam (7d). The **product** (66%) crystallised from methanol as colourless plates, m.p. 251-253 °C (found: C, 62.0; H, 4.8; N, 8.45. $C_{17}H_{16}N_2O_5$ requires C, 62.2; H, 4.85; N, 8.55%); δ 7.8 - 7.4 (m, 4H, ArH), 5.3(d, 1H, 4-H), 3.8(t, 1H, 5-H), 3.7(s, 3H, OMe), 3.6(d, 1H, 1-H), 2.9(s, 3H, NMe) and 1.9(s, 3H, 2-Me); m/z(%) 328(M^+,0.5), 269(100), 184(69), 169(10), 156(10), 91(3) and 77(7).

Lactam 8. Obtained in 60% yield, m.p. 270-271 °C(d). The spectroscopic data were identical to those described above.

We thank Leeds University and Rhône-Poulenc Rorer for support.

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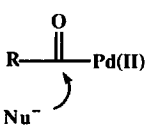
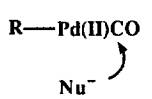
10. Lactam formation could involve either nucleophilic attack on a Pd(II) acyl complex (A) or nucleophilic attack on coordinated carbon monoxide (B).



(A)



(B)

11. Increasing the basicity of the amine results in successive rate enhancements in the expected order: NEt_3 < DBU < t-butyl tetramethylguanidine, Barr, D.A.; Dorrity, M.J.; Grigg, R.; Hargreaves, S.; Malone, J.F.; Montgomery, J.; Rajviroongit, S.; Stevenson, P.; *Tetrahedron*, preceding paper.
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(*Received in UK* 10 *October* 1994; *revised* 25 *October* 1994; *accepted* 28 *October* 1994)